Fibrolamellar Carcinoma: Novel Insights into a Rare Subtype

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We read with interest the retrospective analysis by McDonald et al. utilizing the National Cancer Database (NCDB) and describing the outcomes of 496 patients with fibrolamellar carcinoma (FLC), specifically 229 patients who underwent R0/R1 resection or transplantation.¹ We commend them on aggregating a sizable number of patients with an uncommon tumor histology over an 11-year period, as most reports on FLC are from a single institution and of low volume. McDonald et al. demonstrated poor prognostic factors, such as multiple tumors and positive nodal status, which is consistent with other reported studies; however, they also reported that 44% of FLC patients had elevated α -fetoprotein (AFP), which is significantly higher than the 0–10% previously reported. The authors show a significantly worse prognosis in FLC patients with elevated AFP, which is a novel finding for this rare subtype.

The current study challenges many conclusions that have been made about FLC. The major flaw when comparing normal AFP levels with elevated AFP levels is that they have become dichotomous around the cut-off value of 15 ng/mL. For this reason, an analysis with AFP as a continuous quantitative variable cannot be performed. It would be useful to compare the range of AFP values in both the FLC and hepatocellular carcinoma (HCC) cohorts, as a normal value ranges from 10 to 20 ng/mL and an elevated level was considered to be > 15 ng/mL in the NCDB. The range of AFP values would also give insight into the reasons such a large percentage of FLC patients had elevated values.

The data were compelling in that there was a similar overall survival (OS) compared with a matched resected HCC cohort. This is in contrast to the Surveillance, Epidemiology, and End Results (SEER) database study by Mayo et al., who reported a 32-month improved OS in the surgically managed FLC group compared with the HCC cohort.² On multivariate analysis, McDonald et al. demonstrated that multiple tumors, elevated AFP, and positive lymph nodes were associated with worse survival in the FLC cohort. In addition, FLC patients with elevated AFP had significantly worse survival compared with HCC patients with normal AFP. The FLC patients with elevated AFP consisted of more moderate and poorly differentiated tumors, older patients, and larger tumor size.

The patients for this comparison were matched according to both the Charlson–Deyo Comorbidity Score (CDCS) and resection status; however, patient outcomes in HCC depend on the underlying cause of disease as well as the degree of cirrhosis. The CDCS does include liver disease but it is included as an overall score with other comorbidities and does not specifically measure for the presence of cirrhosis. As a result, the comparison remains unclear as to whether the groups were matched based on the presence of cirrhosis. The authors' findings are consistent with previously published results that conclude cirrhosis is a determining factor in survival. In a meta-analysis that compared FLC versus conventional HCC patients without cirrhosis, Njei et al. demonstrated no difference in survival.³ The subanalysis demonstrating poorly differentiated FLC within the high AFP group does add confusion to the analysis. FLC is histologically well to moderately differentiated despite its paradoxical behavior associated with frequent lymph node metastasis. Poorly differentiated tumors are inconsistent with FLC and may represent a misdiagnosis. As a result, the FLC group with elevated AFP may contain patients with misclassified histology.

We challenge the author's conclusions that AFP may help guide decision making for operative intervention. A poor prognosis has also been demonstrated in HCC with very high AFP levels; however, surgical intervention in HCC typically takes into account liver function and resectability. Most patients with FLC typically undergo R0-intent resection given their healthy liver, along with regional lymphadenectomy for prognostic and possible therapeutic purposes. AFP levels are functional in diagnosis and surveillance but do not usually guide operative intervention.

The authors have demonstrated that AFP can have potential prognostic value in FLC, and have also demonstrated that patients with resected FLC and HCC can have similar survival. However, the role of AFP as a prognostic biomarker in FLC remains unclear, especially with the discrepancy in histology and the lack of baseline liver function data within the NCDB. There may be benefit to recording actual quantitative variables within our large national databases rather than as binary nominal variables (high or low AFP) or aggregate scores (CDCS). The author's conclusions warrant further comparison studies involving FLC, conventional HCC, and its rare subtypes.

DISCLOSURE N. Joseph Espat is a technical consultant to Sirtex, has received speaker honorarium from Sirtex, and is a member of the Medical Advisory Board of IV Diagnostics and Innoblate, none of which have a direct relationship to the topic of our manuscript but are provided for transparency and completeness. Asish Patel and Ponandai Somasundar have no conflicts of interest to declare.

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